



PATENT,  
830010-2006.2

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant : Kolesnikov et al.  
Serial No. : 09/806,645  
Filed : July 15, 1999  
Title : TOPICAL COMPOSITIONS COMPRISING AN  
OPIOID ANALGESIC AND AN NMDA  
ANTAGONIST  
Examiner : L. Wells  
Art Unit : 1617

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*Barnet Shindlerman*  
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**DECLARATION OF GAVRIL PASTERNAK AND  
YURI KOLESNIKOV UNDER 37 C.F.R. §1.131**

Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

We, Gavril Pasternak and Yuri Kolesnikov, hereby declare and state as follows:

1. We are each a citizen of the United States of America and a named inventor in the above-identified application ("the present application" on "the '645 application").
2. We were each an employee of Memorial Sloan-Kettering Cancer Center NY, NY at the time of the conception and reduction to practice of the subject matter of said application.

3. During our employment at Memorial Sloan Kettering Cancer Center, we conceived of the subject matter of U.S. Application Serial No. 09/806,645 ("the '645 application"), in the United States, prior to the January 22, 1997, the effective filing date of U.S. Patent No. 6,008,258, which issued to Inturrisi on December 28, 1999, from U.S. application Serial No. 09/010,239, filed January 21, 1998, with a claim of priority to U.S. provisional application Serial No. 60/035,308, filed January 22, 1997. The '645 application claims priority to U.S. Provisional Application Serial No. 60/092,982 ("the '982 application"), filed on July 16, 1998, as well as to PCT Application No. PCT/US99/16049, filed July 15, 1999.

4. The conception of the subject matter of the '645 application is evidenced, at least in part, by the '982 application, which contains experiments designed and data generated over the course of several months prior to the filing of the application. The conception of the subject matter of the '645 application is also evidenced, at least in part, by protocol designs, reduced to writing in a laboratory notebook, a true copy of which, in redacted form, is attached hereto. The entries in the laboratory notebook (attached) and the work reported therein were performed in the U.S. prior to January 22, 1997. Specifically, the entry states "to test whether ketamine potentiates or blocks and reverses morphine analgesia in tolerance studies."


5. From the time of conception of the invention, we diligently worked upon the invention, including developing additional embodiments of the invention, in the U.S., and promptly and diligently forwarding written descriptions of such additional embodiments to Memorial Sloan Kettering Cancer Center's attorney in the U.S., for the preparation and filing of the '982 application.

6. Thus, the subject matter of the '982 and '645 applications was conceived by us in the U.S. prior to at least January 22, 1997, and was diligently pursued by us until a reduction to practice was achieved on at least July 16, 1998 by the filing of said '982 application (if not earlier as described by the laboratory notebook entry). Accordingly, we are advised and therefore believe that this application is entitled to antedate U.S. Patent No. 6,008,258 within the purview of 37 C.F.R. §1.131. And we respectfully request that U.S. Patent No. 6,008,258 be considered as antedated and as not available as prior art against the instant application.

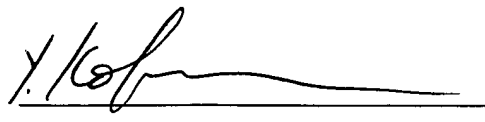
7. We further declare that all statements made herein of own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful, false statements and the like so made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

2/28/03  
Date

  
Gavril Pasternak, Ph.D.

3/3/03  
Date

  
Yuri Kolesnikov, Ph.D.

Combination of topical morphine and ketamine  
 Bupivacaine 0.25% & 0.5% (in 40:1 DMSO)  
 MSalone (1mg/ml) Ketamine (1mg/ml) combination

BL (sec)	Test	BL (sec)	Test	BL	Test
1 2.4	6.4	2.7	4.1	4.1/3.2	10
2.3	4.2	2.8	4.2		
2 2.1	2.6	2.2	2.6	2.6/2.7	4.1/4.2
2.0	3.1	2.1	2.2		
3 2.1	3.8	2.4	3.1	2.4/2.2	4.8/4.9
2.6	3.2	2.2	3.2		
4 2.2	4.1	2.2	4.2	2.5/2.1	5.4/5.6
3.1	4.3	2.8	4.3		
5 3.4	4.8	2.4	6.1	2.7/2.8	6.4/6.5
3.6	5.1	2.6	6.1		
6 2.7	2.7	2.7	2.4	2.4/3.1	3.6/3.8
2.6	3.1	2.8	2.6		
7 2.7	6.1	3.1	2.8	2.6/2.2	2.8/2.9
2.5	3.1	3.2	2.9		
	2.6				
8 2.2	2.7	3.4	4.1	2.3/2.2	4.8/4.9
2.8	2.7	3.5	6.1		
9 2.2	3.2	3.6	4.2	2.4/2.1	4.1/4.2
2.7	3.3	3.7	4.3		
10 1.8	2.9	2.1	2.8	2.4/2.2	4.5/4.1
1.9	2.8	2.6	3.1		
	10.1		10.1		40.1

1. ketamine potentiates morphine analgesia?  
 - to test whether ketamine potentiates or blocks  
 reverse morphine analgesia in tolerance  
 studies

2. to test specific NSAID endpoints in the post-op

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Date: 2/28/2003 11:41 AM

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Subject: SK 865 (FLH 830010-2006.2)

----- Message Contents

Gav and Yuri,

As we have discussed, I came across the Inturrisi patent (attached), which we  
st provide to the patent office to fulfill our duty of disclosure. Fortunately  
our date of invention pre-dates the effective date of this patent as prior art.

To support this conclusion, Yuri has provided me with a notebook page from 19  
6 which shows conception of the invention (that the basic idea was in place and  
being tested). I have attached that page in PDF, having the date redacted, for  
your review.

To antedate this reference and remove it from the examiner's consideration as  
prior art, I have prepared declarations for you to sign. If you agree with the  
statements in the declaration, please sign it and return it to my office (Frommer  
Lawrence & Haug, 745 Fifth Ave, NY, NY 10151).

Please give me a call if you want to discuss this (863-2035) - Amy

Please give me a call if you want to discuss this (863-2035) - Amy

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